Pulmonary Update

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Disclosure of Financial Relationships

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- **Has disclosed relationships with the following entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.**

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Employment: - Medical College of Wisconsin
Consulting Staff: - St. Joseph's Hospital, Milwaukee

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Educational Objectives

What are the important vistas of information that have opened up in Pulmonary Diseases recently?

Asthma
COPD
Pneumonia
Venous Thromboembolism

Asthma

Profile of Asthma Risk Study

Chest 2007; 132:1151-1161.

- Goals of study:
  - 1) Develop clinical tools to identify patients at high-risk for future acute asthma exacerbations;
  - 2) Validate these measures to determine their predictive ability, and;
  - 3) Identify modifiable risk factors.

Profile of Asthma Risk Study

Risk of Future Acute Care

High When Patients…	Low When Patients…
• Have less than normal lung function	
Report: • History of ever receiving acute asthma care; or • Asthma affecting work/school attendance	• Are of younger age • Have better lung function • Are more educated

Chest 2007; 132:1151-1161.

Profile of Asthma Risk Study

Risk of Future Acute Care	
High When Patients…	Low When Patients…

Report:

- Doctor visit for asthma problems in the last year
- Any hospitalization for asthma
- Own a dog/cat*
- Occupational exposures(e.g., solvents)*

* = modifiable risk factors

Chest 2007; 132:1151-1161.

Profile of Asthma Risk Study

- Validation: The three simple clinical models stratified asthmatics into 3 risk groups.
- Pre-bronchodilator $FEV_{1.0}$ was the most significant predictor of subsequent acute care.
- Current cigarette smoking was the strongest modifiable risk factor.
- This classification is easy to use and for most cases, involves a simple clinical questionnaire with or w/o spirometry; skin prick tests can further enhance the results

Bronchial Thermoplasty

- The dynamic state of airway smooth muscle contraction affects airway lumen and thus, causes labile asthma symptoms
- The airway smooth muscle mass influences extent of airway narrowing; reducing this mass can reduce bronchoconstriction
- By delivering controlled thermal energy, bronchial thermoplasty reduces the airway smooth muscle mass, thus reducing the lability and severity of asthma symptoms.
- This article describes the results of a yearlong, randomized controlled asthma intervention research (AIR).

Bronchial Thermoplasty

- **Randomly assigned to Thermoplasty (BTh) or Placebo (Pl) if criteria fulfilled:**
  - Moderate-to-severe asthmatics (n=112)
  - Receiving ICS and Long-Acting β-2 agents (LABA)
  - Demonstrated ↓ on stopping LABA
- **Subjects studied during scheduled LABA withdrawals @ 3 mo., 6 mo. and 12 mo.**

ICS = inhaled corticosteroids; LABA = Long acting β2 agents

Bronchial Thermoplasty

- The study received significant industry support
- Good News:
  - Bronchial thermoplasty improves asthma control in subjects with moderate or severe asthma.
- Bad News:
  - Treatment applied to airways ≥3 mm in diameter
  - Expense, effort, complications and adverse effects would generally preclude its application as a practical therapy for chronic asthma without further modifications

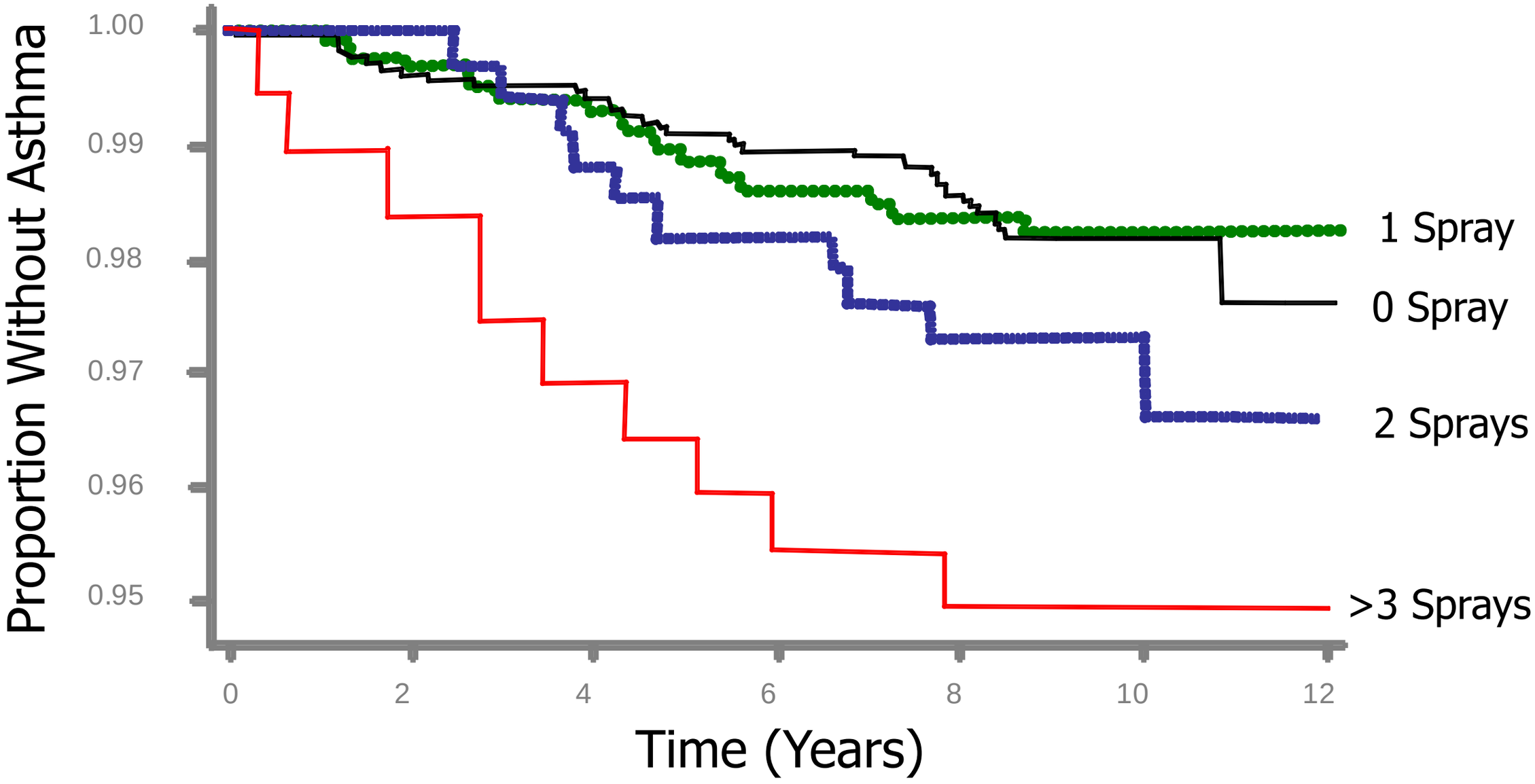
Solway G and Irvin CG (Editorial): N Engl J Med. 2007; 356:1367.

Asthma and Household Cleaners

Zock J, et al. Am J Resp & Crit Care Med 2007; 176:735-741.

- What are the potential risks to the asthmatic from non-occupational exposure to household cleaning agents?

Physician-Diagnosed Asthma According to the No. of Sprays/Day



Asthma and Household Cleaners

Possible Mechanism(s)

- High irritant exposure may cause RADS.
  - Chlorine release on combining bleach and an acid, or chloramine on combining bleach and ammonia
- Chronic low-level irritant exposure may cause airway inflammation
- Sensitization by contents of cleaners
  - e.g., benzylkonium chloride, or chlorhexidine.
- Concurrent exposure to dust and dust mites.
  - Chemical in cleaners might increase reactivity to an allergen

Rosenman KD.: Am J Resp Crit Care Med 2007; 176: 731-734

Montelukast in Asthma Exacerbations

Robertson CF et al. Am J Resp & Crit Care Med 2007; 175:323-329.

- Multi-center, double-blind, randomized trial, pediatric population
- Parent/caregiver given study Rx to be begun upon asthma symptoms/first sign of respiratory tract infection
- Rx given for min. 7 d. or until symptoms resolved for 48 h. up to 20 d.
- Customized asthma Rx plan was also available with β2-agents plus Prednisone.
- Another course of Rx given for the next episode after review of current episode, for of 5 episodes (max).

Montelukast in Asthma Exacerbations

- When given to a child at the onset of acute asthma symptoms, Montelukast:
  - Lowered the rate of acute health care utilization;
  - Reduced the rate of absences from school/daycare;
  - Reduced caregiver's/parent's absences from work; and
  - Reduced sleepless nights for the child

Industry Support: Merck, Sharp and Dohme of Australia funded the study, but the authors say that the protocol was developed independent of the sponsor, as were data management, data analysis, production of the internal study report and preparation of the manuscript.

The PRICE Trial

- Inhaled corticosteroids (ICS) are the preferred anti-inflammatory agent in asthma, but in 25-35% of cases they are ineffective in reducing the bronchial hyperreactivity (BHR) or improving the $FEV_{1.0}$.
- Therefore:
  - What variables predict short-term responsiveness to ICS?
  - How well do these short-term variables predict long-term responsiveness?

Martin RJ, et al. J. Allergy Clin Immunol 2007; 119:73-80.

The PRICE Trial

Responders and Non-responders

	Responders (39)	Non-responders (33)	p value
FEV_1% predicted	68.5±10.4	77.5±8.8	<0.001
FEV_1/FVC	0.65±0.1	0.76±0.1	<0.001

Long-Term (16 weeks)

- Without short-term (6 weeks) response to ICS, continuation or cessation of ICS did not alter asthma control and other secondary outcome measures.
- With short-term (6 weeks) response to ICS, continuation of ICS maintained asthma control and secondary outcome measures
- Correlation was noted between sputum eosinophilia and improvement in $FEV_{1.0}$; however, it was weak (r=0.17).

- Pneumonia

Variables That Define Severe CAP

Uni- and Multi-variate analysis

Socio-demographic	Co-morbidity	Physical Exam	Analytical	Radiographic
Age ≥ 80	CVD	Altered mentation	BUN >30	Pleural fluid
NH Resident		Pulse >125/min	Glucose >250	Multi-lobar/bilateral
		RR >30/min	PaO_2/fiO_2 >250 or PaO_2 <54	
		SBP <90	Arterial pH <7.30	
		T <35° C or >40° C		
Age ≥ 80 **(5)**		SBP <90 **(11)**	Arterial pH <7.30 **(13)**	Multi-lobar/bilateral **(5)**
		RR >30/min **(9)**	BUN >30 **(5)**	
		Altered mentation **(6)**	PaO_2/fiO_2 >250 or PaO_2 <54 **(5)**	

CVD = cerebrovascular disease; fiO_2 = fraction of inspired O_2; NH = nursing home; RR = respiratory rate; SBP = systolic BP

Variables That Define Severe CAP

≥1 Major Criterion	+	≥2 Minor Criteria
•**Arterial pH <7.30** •**Systolic BP <90**		**Mnemonic = CURXO80** • **C**onfusion • **U**rea > 30 mg/dl • **R**espiratory rate >30/minute • **X**-ray multilobar-bilateral • Pa**O**$_2$ < 54 or PaO$_2$/fiO$_2$ <250 mm Hg, and • Age ≥**80**

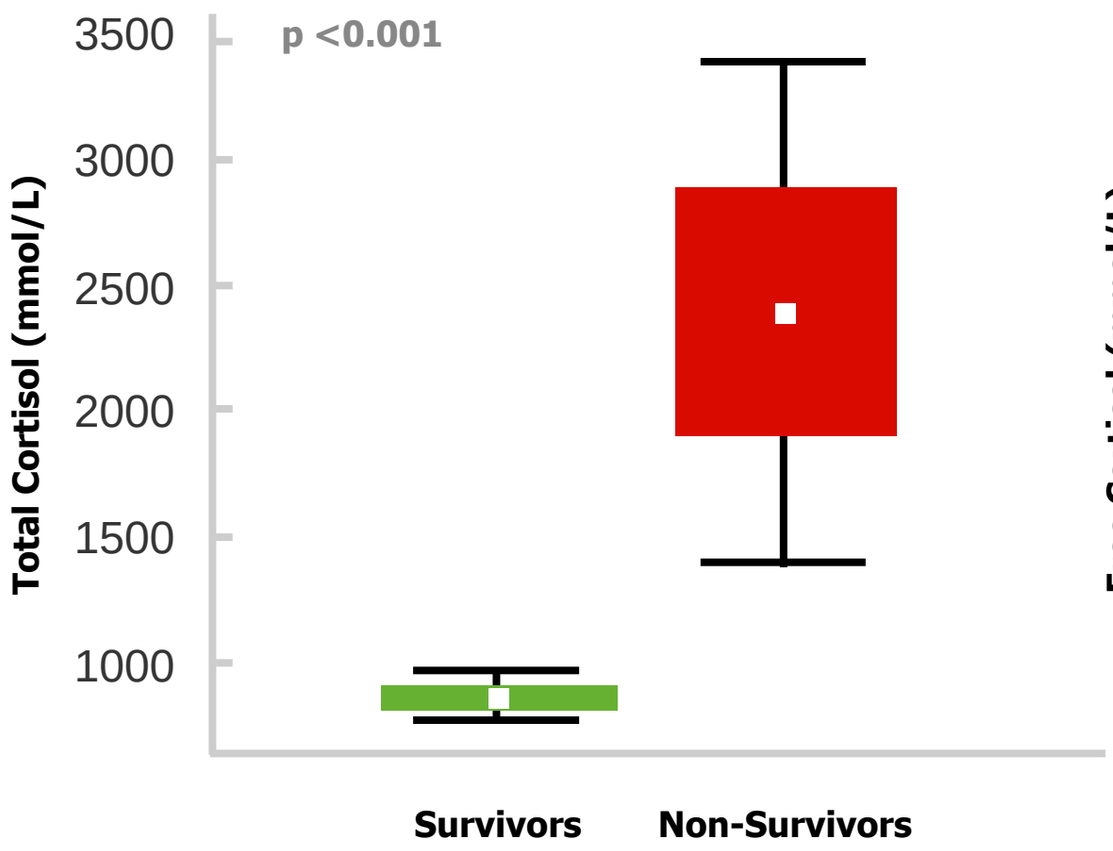
- The above + arterial pH < 7.30 and systemic hypotension with systolic BP < 90 mm Hg indicates Severe CAP.
- The patient should be managed in the Intermediate Care Unit or ICU.
- This approach has 92% sensitivity and 74% specificity.
- The positive predictive value is 21% but the negative predictive value is 99.2%

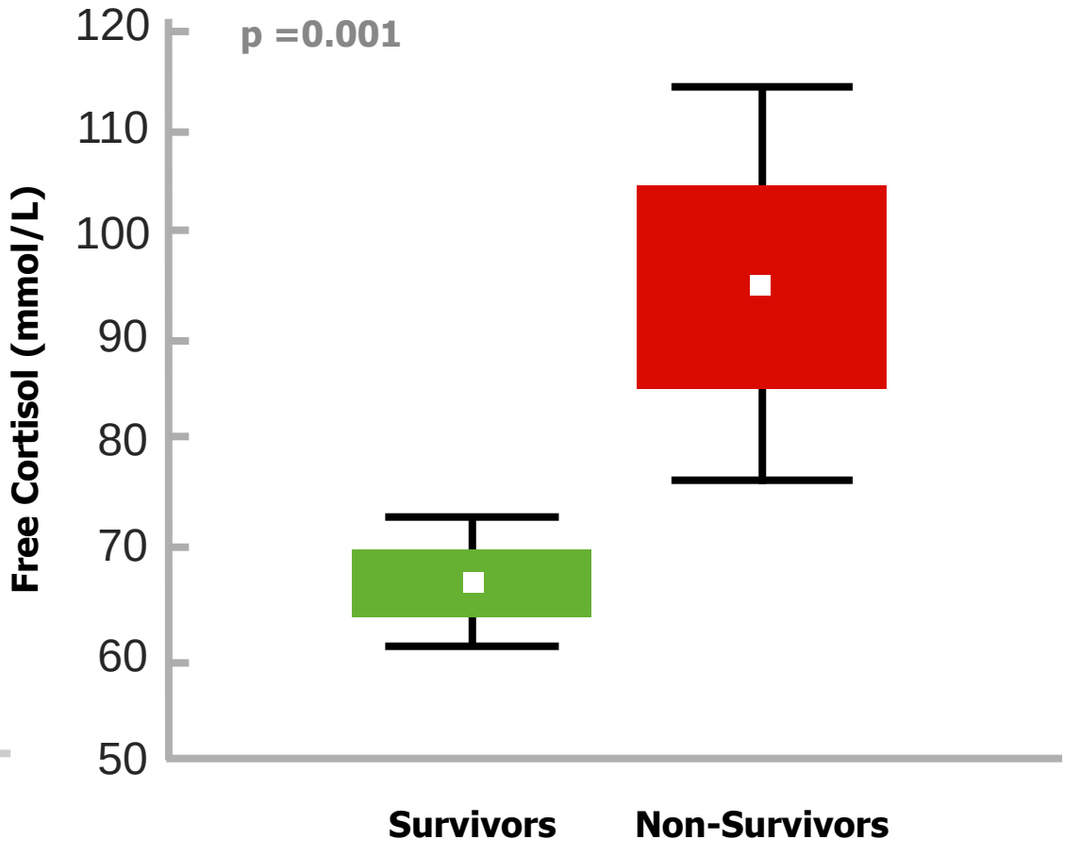
Cortisol Levels and Pneumonia

- In acute illness, free cortisol (FC) levels rise, but the elevation in FC is greater than that in total cortisol (TC) level
- Do FC measurement have any advantages over that of TC?

Am J Respir Crit Care Med 2007; 176: 913–920

Cortisol Levels and Pneumonia Mortality





Cortisol Levels and Pneumonia Mortality

	Cutoff	Sensitivity	Specificity	LR+	LR—
Pneumonia Severity Index	90	96.4	46.2	1.79	0.08
	101	89.3	59.2	2.19	0.18
	134	32.1	87.4	2.56	0.78
Total Cortisol	594	89.3	42.6	1.56	0.25
	960	75.0	71.7	1.65	0.35
	1650	42.9	88.8	3.82	0.64

LR+ = Positive Likelihood Ratio; LR— = Negative Likelihood Ratio

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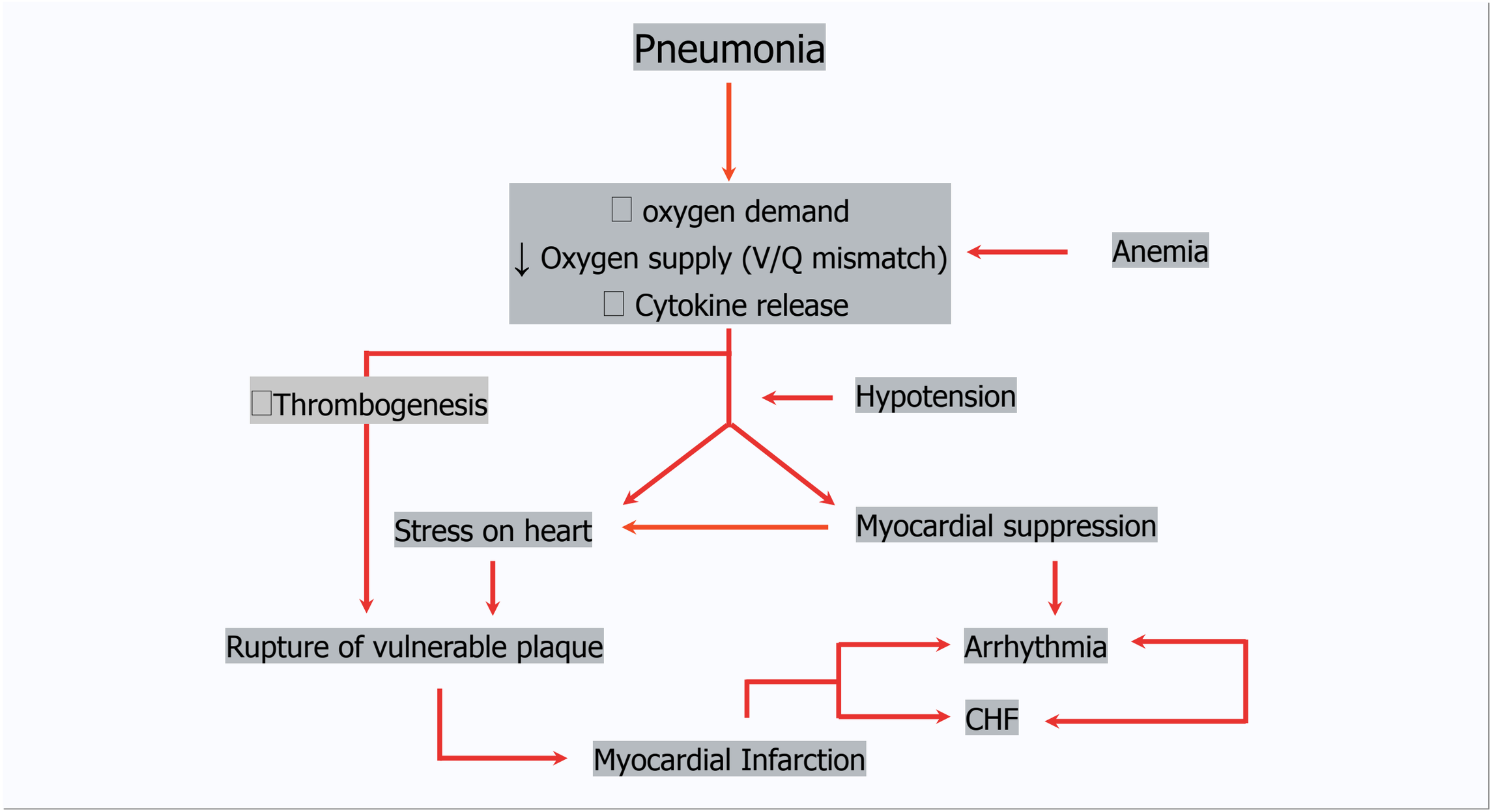
Pneumococcal Pneumonia and Acute Cardiac Events



Clin Infect Dis 2007; 45:158-165.

Pneumococcal Pneumonia and Acute Cardiac Events

- Total with cardiac events: 33/170
- Eleven of 33 were in Class IV and 20 were in Class V by PSI
- All 33 had at least one cardiac event at admission
- Ten of 33 had pneumococcal bacteremia

Clin Infect Dis 2007; 45:158-165.

Pneumococcal Pneumonia and Acute Cardiac Events

Event	No. (%) of patients	No. with Hypoxemia	No. with Anemia
Myocardial infarction	**12 (7.1)**	**12/12**	**7/12**
New arrhythmia	2 (1.1)		
New or worsening CHF	5 (2.9)		
New arrhythmia	**8 (4.7)**	**7/8**	**3/8**
New or worsening CHF	6 (3.5)		
New or worsening CHF	**13 (7.6)**	**9/13**	**6/13**
Total Patients with Cardiac Event	**33 (19.4)**		
		Hypoxemia	**Anemia**
Total No. of Cardiac Events	**46**	**28/33**	**16/33**

Clin Infect Dis 2007; 45:158-165.

Pneumococcal Pneumonia and Acute Cardiac Events

Conclusions and Limitations

- **Conclusions**
- Significant cardiac complications accompany pneumonia
- This poses an important clinical risk
- Concurrent anemia or hypoxemia worsens this risk.
- Pneumonia in those with known heart disease should be treated with extreme caution
  - Close observation necessary for the complications described.
- **Limitation**
- Retrospective study from institution with high smoking prevalence
  - Possibly increased CAD risk
  - The authors concluded that this was not a serious/significant.

Clin Infect Dis 2007; 45:158-165.

- Chronic Obstructive Pulmonary Disease

GOLD Classification of COPD Severity

From: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary updated 2006. http://www.goldcopd.com.

Stage	Severity	FEV1/FVC	Post-dilator FEV1
I	Mild	<0.70	≥80%
II	Moderate	<0.70	<80%
III	Severe	<0.70	<50%
IV	Very Severe	<0.70	<30..50%+

Stage 0 (zero), unlike in previous versions, is no longer used

+ : When FEV1 50%, chronic respiratory failure necessary to qualify for Stage IV

Combination Inhaler Therapy for COPD

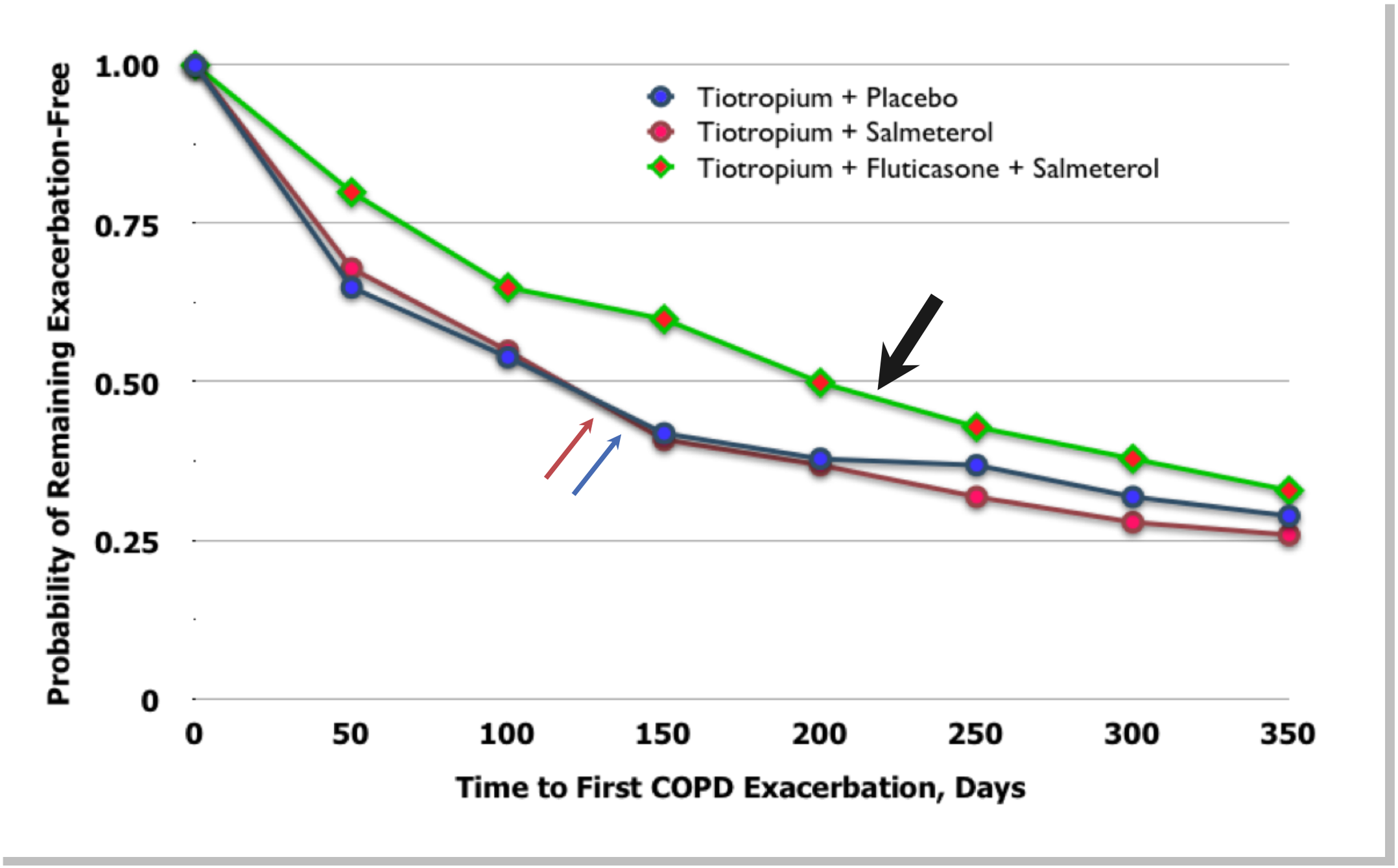
Primary Outcome

	TSF	TS	TP
Proportion of Pts. w. ≥1 exacerbation	60%	64.8%	62.8%
Absolute Risk Reduction	2.8%	-2.0%	
95% CI	8.2-13.8	12.8-8.8	
p	0.62	0.71	
Unadjusted OR of risk of exacerbation	0.85	1.03	
95% CI	0.52-1.38	0.63-1.67	
Adjusted OR of risk of exacerbation	0.84	1.01	
95% CI	0.47-1.49	0.59-1.73	
IRR (Alternative compliance analysis)	0.79	1.07	
95% CI	0.54-1.14	0.74-1.55	
p	0.21	0.71	

IRR = Incidence rate ratio; OR = Odds ratio; TP = Tiotropium plus placebo; TS = Tiotropium plus Salmeterol; TSF = Tiotropium plus Salmeterol plus Fluticasone.

Ann Intern Med 2007; 146:545-555.

Combination Inhaler Therapy for COPD



Aaron SD at al. Ann Intern Med 2007; 146: 545-555

So……

- A triple regimen of Tiotropium, Salmeterol and Fluticasone improved spirometry and quality of life;
- The time it took for the first exacerbation was the highest with the triple regimen, but this was not statistically significant.
- The decrease exacerbation rates was not statistically significant for any particular combination.

Ann Intern Med 2007; 146:545-555

However.....

- Many patients receiving Tiotropium plus placebo and Tiotropium plus Salmeterol prematurely stopped therapy; many crossed over to treatment with open label inhaled corticosteroids or long-acting beta-agents (total 40%);
- The study was funded by the Canadian Institute for Health Research and the Ontario Thoracic Society. Many authors had affiliations with the pharmaceutical industry.

Ann Intern Med 2007; 146:545-555

Does Combination Inhaler Therapy for COPD Improve Survival?

- This is the Towards a Revolution in COPD Health (TORCH) trial
- Primary Outcome:
  - Death from any cause
- Secondary Outcomes:
  - Frequency of exacerbations
  - Health status
  - Spirometric values.

N Engl J Med 2007; 356:775-789.

TORCH Says...

Conclusions

- ICS-LABA combination reduced COPD exacerbations significantly, including those requiring hospitalization and improved quality of life and spirometry.
- Mortality reductions were not statistically significant
- Fluticasone-containing regimens seem to predispose patients to a higher risk for pneumonias

The study was heavily supported by industry and many authors had significant relations with the industry

N Engl J Med 2007; 356:775-789.

Preventing COPD Exacerbations by LABA and ICS or Tiotropium

- Study published in 2008
- Pts. receiving LABA + ICS were less likely to withdraw, had better health status and better survival.
- There were twice as many cases of pneumonia in the combination group compared to tiotropium.

The study was heavily supported by industry and many authors had significant relations with the industry

Wedzicha JA et al. Am J Resp Crit Care Med 2008; 177:19-26.

COPD Exacerbation: Does Steroid Route Make a Difference?

- Hospitalized patients with AE-COPD receive glucocorticoids generally intravenously.
- The objectives were to determine if oral glucocorticoids were not inferior to IV glucocorticoids in AE-COPD.
  - A determination of their equivalency is not available in the adult literature in this clinical context

Chest 2007; 132:1741-1747.

COPD Exacerbation: Does Steroid Route Make a Difference?

Primary Outcome	IV	Oral	95% CI Lower Bound
All Treatment Failures			
Total	66 (61.7%)	58 (56.3%)	-5.8%
Death	5	2	
Hospital Readmission for COPD	13	11	
Intensification of Pharm Rx	48	45	

Chest 2007; 132:1741-1747.

COPD Exacerbation: Does Steroid Route Make a Difference?

Conclusions

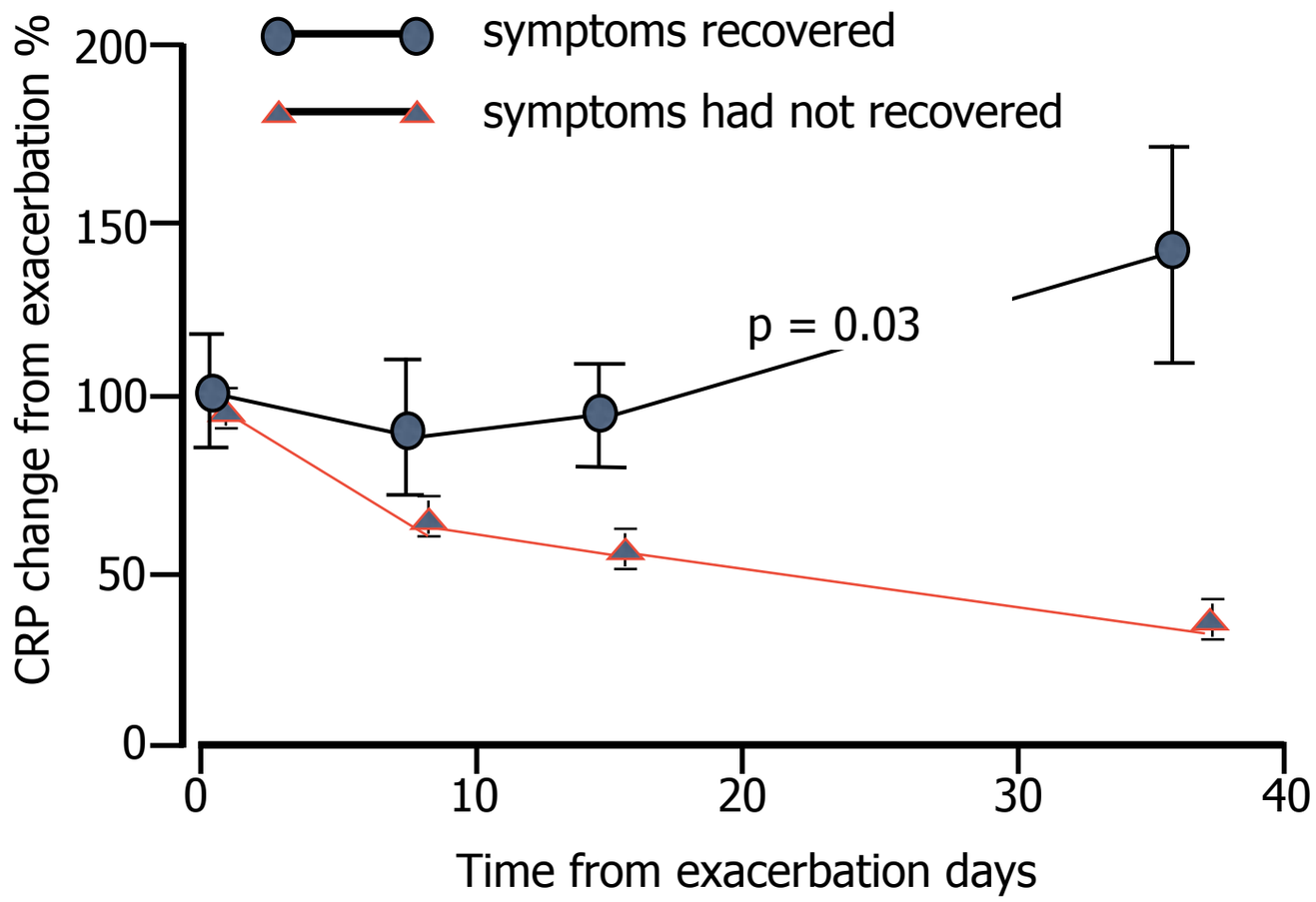
- Oral Prednisolone is not inferior to IV Prednisolone in treating moderate-to-severe or less-than-very-severe COPD exacerbations
- Overall failure rate is higher in the present study, compared to older studies.

Chest 2007; 132:1741-1747.

Clinical Correlates of Airway Inflammation in COPD Exacerbation

- COPD exacerbations are accompanied by airway and systemic inflammation
- The correlates of the inflammation to recovery from and recurrences of exacerbations are not understood
- Serum and sputum interleukin-6 (IL) and IL-8 and serum C-reactive protein (CRP) may serve as surrogate markers
- The authors evaluated the role of these markers in predicting recovery from and occurrence of AE-COPD.

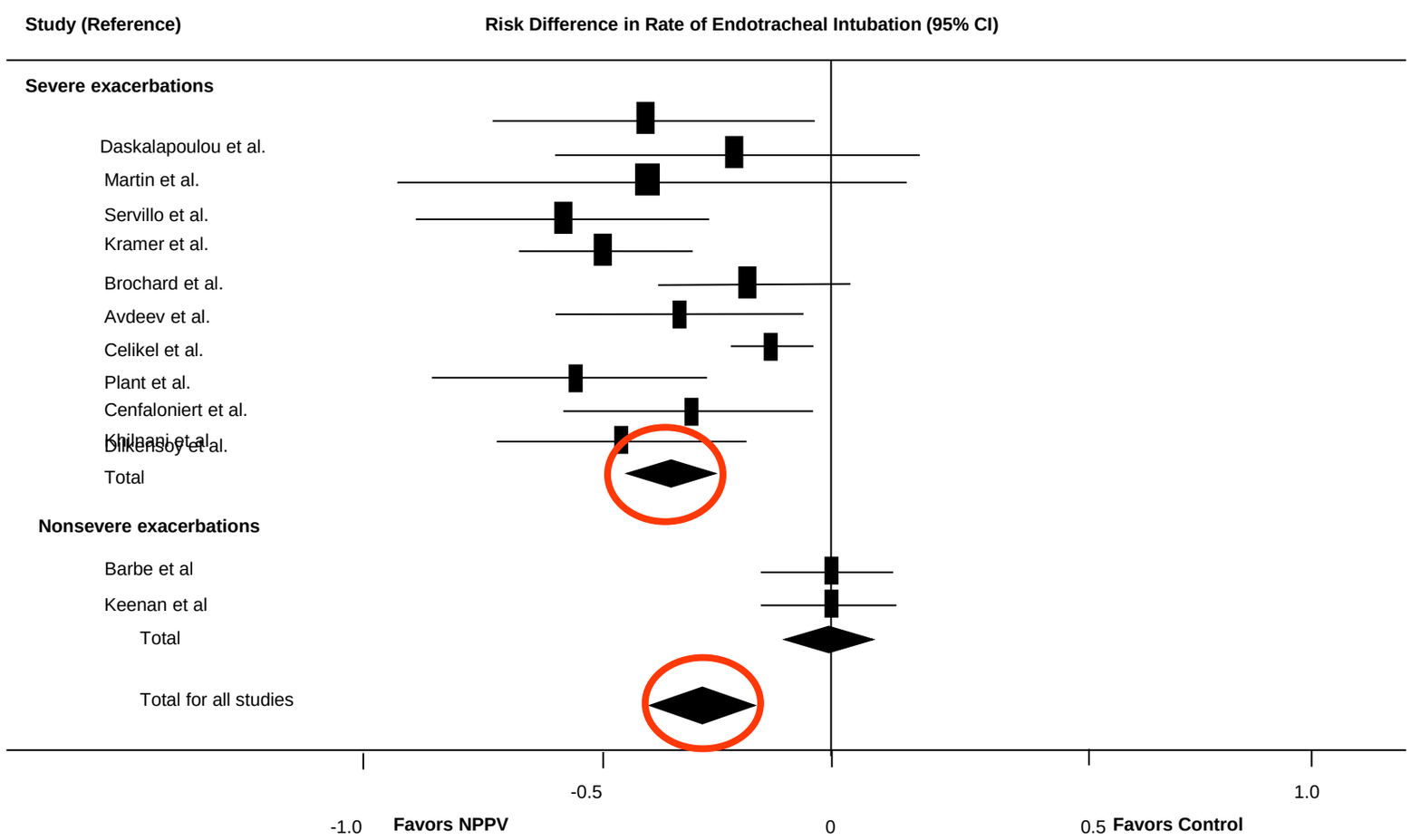
Airway Inflammation in COPD Exacerbation



Airway Inflammation in COPD Exacerbation

- So, what does this study tell us?
  - First, COPD exacerbation is a systemic inflammatory process
  - Inflammatory markers decline within a few days of the exacerbation onset indicating resolution
  - Persistent elevation correlates with incomplete resolution of symptoms and foretells an oncoming event
  - This knowledge could help us prognosticate better and develop better therapeutic strategies
  - Those with frequent exacerbations have a reduced response to therapy, which results in persistently higher systemic inflammatory markers and which may explain the greater decline in lung function observed in these patients.

Noninvasive Positive Pressure Therapy for COPD Exacerbations



Keenan SP et al.: Ann Intern Med 2003; 138:861-870

- Venous Thromboembolism

VTE Prophylaxis in Acutely Ill Hospitalized Patients

- **I**nternational **M**edical **P**revention **R**egistry **o**n **Ve**nous Thromboembolism (IMPROVE) is an ongoing, multinational, observational study

- It is designed to assess VTE prophylaxis in acute care settings and to examine the outcomes

- Data abstracted: patient demographics; underlying medical Dx; types, duration and timing of VTE prophylaxis and hospital discharge disposition

Chest 2007; 132:936-945

VTE Prophylaxis in Acutely Ill Hospitalized Patients

Characteristics	Any	LMWH	UFH	IPC	ES	ASA	Other
IMPROVE population*	50	34	11	5	6	2	2
Medical Condition							
Current cancer	45	31	9	7	4	0.9	2
ICU stay	77	41	25	19	8	2	5
CHF (NYHA III or IV)	64	43	16	6	5	3	4
Obesity	57	34	16	8	7	2	3

(n= 15,156)

Chest 2007; 132:936-945

Anticoagulant Prophylaxis in Hospitalized Medical Patients

- Anticoagulant prophylaxis the risk for symptomatic non-fatal and fatal VTE in hospitalized medical patients who are at risk for VTE.
- During treatment risk of symptomatic PE was □ by 58% and that of fatal PE by 64%;
- The risk for symptomatic DVT was by 53% but all-cause mortality was unchanged;
- One would need to prophylactically anticoagulate 345 hospitalized medical patients at risk for VTE to prevent 1 symptomatic PE and 400 patients to prevent 1 death due to PE.
- Routine anticoagulant prophylaxis causes a 32% relative risk increase (or .14% absolute risk increase) of major bleeding. The potential cost is also substantial, because of the 7 million at-risk medical patients hospitalized annually who would now be candidates for VTE prophylaxis.

- *Five of the 9 studies were industry-supported but this did not seem to affect the outcomes.*

Dentali F et al.: Ann Intern Med 2007;146: 278-288

Echocardiographic and Functional Cardiopulmonary Problems 6 Months After First-time PE in Previously Healthy Patients

Initial Echocardiogram	
Normal RV (61)	Abnormal RV (61)
	Dilatation (28)
	Hypokinesis (3)
	Both dilatation and hypokinesis (30)
Six-Month Follow Up Echocardiogram	
Normal (82)	Abnormal (27)
	Dilatation (21)
	Hypokinesis (2)
	Both dilatation and hypokinesis (4)
Functional Limitation at 6 months (27)	
	6MWD <330M (12)
	NYHA Score >II (6)
	Both 6MWD <330M and NYHA Score >II (9)

Eur Heart J. 2007;28:2517-2524

Echocardiographic and Functional Cardiopulmonary Problems 6 Months After First-time PE in Previously Healthy Patients

- These data suggest that pulmonary embolism causes protracted loss of RV function in a subset of patients.
  - The authors attribute this to ischemic and structural RV injury followed by inflammation.
  - In a similar number of patients, the quality of life had dwindled.
- The echocardiogram was at best modestly predictive of such poor outcomes, with a sensitivity 62% and overall accuracy of 57%.
- No bio-marker (homocysteine, anti-cardiolipin, beta-2 glycoprotein antibody, Factor V Leiden mutation, MTF reductase mutation, etc.) successfully predicted outcome.
- A higher proportion of cases with RV dysfunction had positive Lupus anticoagulant test.

- These observations require further validation

Eur Heart J. 2007;28:2517-2524

- Pulmonary Embolism Causing Acute COPD EXacerbations

Results of Spiral CT Angiography in Patients With COPD Exacerbations of Unknown Cause

Symptoms	Patients with COPD (n = 197)
Presence of PE, n (%)	43 (22)
Central, n (%)	20 (46)
Segmental, n (%)	21 (49)
Isolated Subsegmental, n (%)	2 (5)
Absence of PE, n (%)	154 (78)
CT negative to segmental level, n	84
CT negative to subsegmental level, n	70

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; CT = Computed Tomography; PE = Pulmonary Embolism

To Sum Up.....

- We now have a simple clinical instrument that can be tailored and that could stratify asthmatics into risk groups that predict the need for future acute care.
- Bronchial thermoplasty improves asthma control in moderate or severe asthma but serious practical problems plague its wide application.
- Exposure to household cleaners is a factor to be reckoned with in causing/worsening asthma
- Montelukast reduces the severity of episodes and healthcare utilization in children when given at the onset of exacerbation

To Sum Up……

- The use of a simple 6 weeks' trial of ICS based on $FEV_{1.0}$ change appears to be a good indicator of longer-term asthma control
- Using fewer variables, it might be possible to predict the severity of community acquired pneumonia in the Emergency Department
- Total Cortisol level on admission might predict severity and mortality in community acquired pneumonia
- A stronger relationship seems to be emerging between pneumonia and cardiac complications of myocardial infarction, heart failure and arrhythmias
- A combination of tiotropium, fluticasone and salmeterol improves spirometry and quality of life in COPD and might help reduce/prolong exacerbations

To Sum Up……

- ICS-LABA combination reduces COPD exacerbations significantly, including those requiring hospitalization and improves quality of life and spirometry.
- Fluticasone-containing regimens seem to predispose to a higher risk for pneumonias
- Oral Prednisolone is not inferior to IV Prednisolone in treating moderate-to-severe or less-than-very-severe COPD exacerbations
- There might be a role for biomarkers in the evaluation, treatment and prognostication of COPD Exacerbations
- DVT prophylaxis needs to be more widely used in medical patients and its role better defined and possibly extended.

To Sum Up…

- We need a valid risk-classification scheme to identify patient groups with high VTE risk to warrant, or lower-risk groups to avoid, VTE prophylaxis.
- Submassive pulmonary embolism causes protracted loss of RV function and reduces quality of life in a subset of patients; there are no effective ways to identify them at present.
- In a significant number of patients with COPD exacerbation, pulmonary embolism plays a critical role in their genesis.

- Thank you for listening

The Rising Mortality of COPD